

PARACETAMOL POISONING

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Paracetamol poisoning was first reported⁽¹⁾ in the medical literature about a hundred years ago. However, it is only in the last forty years when the use of the phenacetin group of analgesics has gained tremendous popularity that overdosages of this drug have been encountered ever so often. Its availability as an over-the-counter drug has also contributed significantly to its intake in overdosage.

There is little information available on the true incidence of paracetamol overdosage in any country or the mortality and morbidity associated with it. Sixty-six such deaths were reported in Great Britain in 1973⁽¹⁾. In United States, the number of reported deaths from acetaminophen overdosage from 1973 to 1975 fell from 2.1 per 1,000 cases of overdosage to 0.85 per thousand⁽²⁾. This has been despite a nearly three-fold increase in the incidence of overdosage.

Since liver damage associated with paracetamol was first reported by Davidson DGD and Eastham WN of the UK in 1966⁽³⁾, many other larger series⁽⁴⁻⁷⁾ have appeared in the literature. Rumack BH and Peterson RG⁽²⁾ reported 112 cases of hepatic toxicity out of 416 cases of acetaminophen overdosage (26.9%). A study of cases seen at the Prince of Wales Hospital in Hong Kong⁽⁸⁾ revealed only 4 subjects out of 76 (5.3%). No such study has been done in Singapore, but it would be interesting to find out the pattern of paracetamol overdosage in this country.

The mechanism of paracetamol induced hepatotoxicity is confusing to many. It can, however, be easily explained in the following steps:

- (1) A small proportion of an ingested amount of paracetamol is acted upon by the cytochrome P450 dependent mixed-function oxidase enzymes present in liver cells and converted to a reactive metabolite.
- (2) After therapeutic doses of paracetamol, the small amount of reactive metabolite produced is detoxified by conjugation with cellular glutathione and excreted in the urine as cysteine and mercapturic acid metabolites.
- (3) In paracetamol overdosage, there is excessive formation of reactive metabolite.
- (4) If the large amount of reactive metabolite depletes cellular glutathione stores by at least 70%, then detoxification slows down.
- (5) The non-detoxified reactive metabolite undergoes covalent bonding to protein macromolecules in the hepatic cell and arylates the nucleophiles in the cell resulting in hepatic cellular necrosis.

Inducers of the cytochrome P-450 enzymes, such as barbiturates and diphenhydramine increase the formation of the

reactive metabolite and are more likely to contribute to hepatocellular necrosis in the presence of paracetamol overdosage. Evidence as to the positive effect of ethanol and malnourishment on paracetamol hepatotoxicity^(9,10) is at best controversial.

Recently, Mitchell et al⁽¹¹⁾ have reported that the hepatic injury produced by the arylated nucleophiles also leads to a rapid increase in neutrophil accumulation with a consequent plugging of the hepatic microvasculature. These secondary microcirculatory changes exacerbate the original injury and expand the region of necrosis through an ischaemic infarction of the periportal region.

Over the years, serum levels of paracetamol measured at least four hours after ingestion have come to be regarded as the final arbiter of need for antidote therapy in the management of suspected paracetamol overdosage. This has been owing to the following⁽²⁾:

- (1) Lack of correlation between the historical amount of ingested paracetamol and toxicity.
- (2) Peak plasma concentrations are not thought to occur till at least two hours after ingestion and delayed peaks may occur because of delayed gastric emptying that may occur in overdosage situations.
- (3) A large proportion of overdosed patients do not turn up till at least more than 2-3 hours post ingestion.

As a result, normograms have been developed by different groups^(12,13) to determine if measured levels of paracetamol in the blood are consistent with toxicity. This is to decide on the need for administration of antidotes which though relatively safe have been associated with some unpleasant and sometimes unacceptable side effects. Though these normograms are of use, the principal treatment modes for paracetamol overdosage have to be initiated immediately and there is a lag time of 1 to 4 hours or even longer for such levels to be known depending on the timeliness of the investigative resources available to the local medical institution. Antidotes also lose their effectiveness if instituted late. Accurate and timely diagnosis of paracetamol toxicity is essential for optimal management. Recently, a 30-second test kit using an Acetaminophen Test Meter⁽¹⁴⁾ has been developed. If proven effective and reliable, this should be a significant advancement in the management of patients with paracetamol overdosage. However, timing of ingestion of paracetamol may frequently be unclear, in which case initial serum paracetamol levels greater than 10 µg/ml should prompt initiation of antidote therapy.

The initial management of paracetamol overdosage should be at the Emergency Department rather than at the inpatient ward for obvious reasons. It has, however, been the traditional practice in many institutions that all definitive forms of therapy for poisoning be carried out after an inpatient bed had been found for the patient, the admission procedures completed, the patient transported to the inpatient ward, clerked by the house-officer and perhaps even reviewed by the resident medical officer-on-duty (an average delay of one to four hours). Once a diagnosis of paracetamol toxicity has been made, initial man-

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agement at the Emergency Department should consist of the following:

(1) Gastro-intestinal decontamination

This should begin with gastric lavage. In paracetamol overdosage, gastric lavage, to be effective, has to be carried out within four hours of ingestion, though with mixed intoxications a longer period of up to 6 hours may allow removal of residual paracetamol in the stomach. The tube used should be a large-bore gastric lavage tube, rather than a narrow-bore Ryles' tube, for effective removal of particulate matter.

Activated charcoal (AC) has gained an important role in gastrointestinal decontamination after paracetamol overdosage. AC is the residue from the destructive distillation of various organic materials. It has the unique property of being able to act as an adsorbent of many chemical substances. The adsorptive power of charcoal has been increased or "activated" by specific treatment to increase its surface area to about 950 sq metres/gm in the case of standard AC and 2500 to 3000 sq metres/gm for superactivated charcoal⁽¹⁵⁾. Paracetamol is readily adsorbed into AC⁽¹⁶⁾, especially if the first dose of AC is given within 4 hours of ingestion. This will decrease the amount of paracetamol absorbed into the circulation. AC has also been noted to have a gastrointestinal dialysis effect on paracetamol resulting in passive diffusion of drug from serum into the lumen of the gastrointestinal tract. The usual initial dosage of AC for adults is 25 to 50 gm in 100 to 200 ml water (0.5 - 1 gm per kg body weight). This initial dose may be mixed with a cathartic such as sorbitol or magnesium sulphate. It is believed that repetitive oral doses of AC will enhance the prevention of gastrointestinal absorption of paracetamol.

(2) Antidotes

Together with measures to enhance gastrointestinal elimination of the ingested drug, the emphasis is on treatment of the hepatotoxic effects⁽¹⁷⁾. Since it is the relative scarcity of sulphhydryl groups that leads to the process causing hepato-cellular damage definitive therapy has been directed at measures to increase their availability.

The first agents that were used were cysteamine and methionine and these gave encouraging results. However, both produced a fair bit of side effects and methionine was less effective. These led to trials with N-acetyl cysteine (NAC) which emerged as the preferred treatment.

The efficacy of NAC has been explained through four possible mechanisms:

- (a) acting intracellularly as a glutathione substitute⁽¹⁸⁾,
- (b) enhancing synthesis of additional glutathione,⁽¹⁹⁾
- (c) providing substrate to enhance the non-toxic sulphation pathway of paracetamol metabolism⁽²⁰⁾,
- (d) acting as an anti-oxidant to abrogate the accumulation of neutrophils and the secondary effects on the hepatic microvasculature⁽¹¹⁾.

Two principal modes of NAC administration have been advocated, viz oral and intravenous.

The use of oral NAC (or Mucomyst) has been mainly in the USA. A total dose of 1330 mg⁽²¹⁾ is given over a 72-hour period with treatment sometimes begun as late as 24 hours after ingestion. There are currently no data to show that the incidence of paracetamol hepatotoxicity is greater with oral antidotes as opposed to intravenous antidotes. The main problems with oral antidote therapy have been in the initial phase of management. For patients in whom syrup of ipecac has been used as an initial mode of gastrointestinal decontamination, no other oral drug can be effectively administered until

the emetic effects of Ipecac Syrup have subsided which may take up to one or one and a half hours. This delays administration of antidote.

In addition, paracetamol poisoning also manifests as nausea and vomiting and even without the use of Ipecac Syrup, orally administered Mucomyst may not be available for gastrointestinal absorption and therefore not always practical.

For those patients who had gastrointestinal decontamination by AC, there is conflicting evidence on the binding capacity of AC for orally administered NAC. This has led to differences⁽²²⁾ in the protocols for initial management of paracetamol overdosage in the USA.

Such a dilemma does not seem to exist for intravenously administered NAC - the use of which has been common in the member countries of the British Commonwealth (including Singapore) and in Europe. A 20-hour regime giving a total of 300 mg/kg over a 20-hour period is often used in these countries. A 48-hour intravenous regime⁽²⁴⁾ using a total of 910 mg/kg over 48 hours was tried out in the USA and better results are claimed than for the 20-hour regime. With all these regimes, flushing, urticaria, hypotension and bronchospasm have been rarely reported shortly after starting treatment, at a time when the concentrations of NAC are highest. These effects therefore appear to be concentration-dependent⁽²⁵⁾. It is likely that smaller doses or shorter duration of treatment may be at least as efficacious.

Whatever the optimal regime for use of NAC, time of initiation of therapy is of the essence. A large study of 11,195 cases of suspected paracetamol overdosage by Smilkstein et al⁽²¹⁾ described the outcome of 2,540 patients in whom oral NAC was used. Hepatotoxicity was reported in 6.1% of patients in whom NAC was started within 10 hours of ingestion and 26.4% when therapy was started between 10 and 24 hours after ingestion. In the high risk group treated between 16 to 24 hours after ingestion, 41.0% developed hepatotoxicity. NAC does not seem to confer any benefit if initiated more than 24 hours after ingestion. More careful analysis will therefore be required of those studies claiming greater efficacy of continuation of NAC therapy beyond 24 hours.

In addition to the treatment regimes mentioned above, other therapeutic modalities have been previously suggested. Forced diuresis has been tried but does not appreciably hasten elimination as only 5% of the unaltered drug is excreted in the urine⁽²³⁾. Haemodialysis, though able to reduce the half-life of paracetamol has not been shown to appreciably affect the clinical outcome. Administration of high-dose steroids and exchange transfusion have all been done with no appreciable benefit. The use of liver transplantation as an alternate form of therapy in severe hepatic necrosis is still experimental.

One interesting recent development has been the finding of secondary microvascular changes mentioned earlier⁽¹¹⁾. These changes may be completely prevented by treatment with antioxidants such as allopurinol. The final word has not been said yet of the management of paracetamol overdosage. Further understanding of all the microcellular and biochemical changes that accompany paracetamol overdosage will lead to newer treatment modalities that will decrease the incidence of hepatotoxicity and hence morbidity of paracetamol overdosage.

Being an extremely common and easily available over-the-counter drug, paracetamol will continue to be frequently abused. Short of restricting access to this extremely useful medicinal agent, future directions in management of paracetamol overdosage may be in attempts to completely prevent hepatotoxic effects. Efforts have already begun in Norway and Finland⁽²⁶⁾ to reduce hepatotoxicity by marketing paracetamol as paracetamol/methionine or methionine ester combinations.

The relative safety and efficacy of such combinations need to be further assessed.

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